Pathologic Response After Neoadjuvant Carboplatin and Weekly Paclitaxel for Early-Stage Lung Cancer

A Brown University Oncology Group Phase II Study

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Introduction: Pathologic complete response (pCR) to neoadjuvant chemotherapy is associated with improved survival in solid tumors. Southwest Oncology Group 9900 demonstrated a 9% pCR after three cycles of paclitaxel/carboplatin every 21 days. We evaluated pCR rate with intensive weekly paclitaxel in a phase II study.

Methods: Patients with non-small cell lung cancer, stage IB to IIIA, were eligible and received carboplatin, area under the curve = 6, every 21 days ×3 and paclitaxel 80 mg/m^2 weekly ×9. Primary outcome was the pCR rate.

Results: Twenty patients with clinical stage IB (n = 16), IIA (n = 1), IIB (n = 1), and IIIA (n = 2) were enrolled. Mean age was 65 years. Toxicity included grade 4 neutropenia in 1 (5%), grade 3 neutropenia in 3 (15%), grade 3 neuropathy in 1 (5%), and grade 3 nausea in 1 (5%). After neoadjuvant therapy, one patient refused surgery and one died of a nontreatment-related event. Eighteen patients underwent complete resection, 15 by lobectomy, and 3 by pneumonectomy. Pathology revealed 3 (17%) patients with pCR. The median follow-up is 67 months. For clinical stage IB (n = 16), the median overall survival has not been reached, and the 5-year overall survival is 69%. All patients with pCR (n = 3) remain alive and disease-free. Improved overall survival was seen in patients who were pathologically down-staged versus patients who were not, p = 0.05.

Conclusions: Neoadjuvant chemotherapy with intensive weekly paclitaxel and carboplatin is well tolerated and does not increase surgical morbidity. This intense regimen achieves rates of pCR and survival that compares favorably with other reported induction regimens and merits further investigation.

Key Words: Adjuvant/neoadjuvant therapy, Lung cancer clinical trials, Lung cancer surgery.

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Lung cancer is the leading cause of cancer-related death in North America.[1] Despite curative resection for early stages I and II, 5-year survival ranges from only 39 to 67%.[2] Recurrence most commonly occurs at distant sites, emphasizing the need for systemic therapeutic approaches to improve cure rates.

Chemotherapy after surgical resection for lung cancer has been shown to be beneficial in randomized trials.[3,4] However, chemotherapy compliance in the postoperative setting continues to be poor.[5] Chemotherapy delivered before surgery has been shown to have good compliance and with the promising data of paclitaxel used in a weekly regimen, the Brown University Oncology Group sought to evaluate the preoperative delivery of weekly paclitaxel in combination with carboplatin for early-stage non-small cell lung cancer in a phase II trial.

MATERIALS AND METHODS

Inclusion criteria for the Brown University Oncology Group phase II trial included biopsy proven non-small cell lung cancer, age 18 years or older, clinical stage IB to IIIA (minimal or nonbulky N2 disease), and postoperative predicted forced expiratory volume in 1 second ≥40%. Eligible patients underwent imaging with computerized tomography scan, magnetic resonant imaging of the brain, and positron emission tomography scan. All patients underwent routine cervical mediastinoscopy.

Neoadjuvant chemotherapy consisted of paclitaxel 80 mg/m^2 given every week ×9 and carboplatin, AUC = 6, given every 3 weeks ×3. Computerized tomography scan was performed after chemotherapy to measure clinical response. Surgery was performed 2 to 6 weeks after chemotherapy. At surgery, the minimum extent of resection was lobectomy along with mediastinal lymph node dissection.

Staging was according to American Joint Committee on Cancer Staging 6th edition.[2] Chemotherapy toxicity was graded based on the National Cancer Institute Common Toxicity Criteria for Adverse Events v3.0.[6] Clinical response was assessed using the Response Evaluation Criteria in Solid Tumors guidelines.[7] The primary outcome of this trial was the rate of pathologic complete response (pCR). Due to the importance of pCR in our trial, the entire primary tumor and all mediastinal nodes were submitted for pathologic analysis

TABLE 1. Patient Characteristics ($n = 20$)

Characteristic	
Gender	
Male	8 (40)
Female	12 (60)
Age (yr)	65 (47–76)
FEV1 (L)	2.13 (1.12–3.51)
% Predicted FEV1	89 (59–124)
% Predicted DLCO	86 (34–121)
Extent of resection[a]	
Lobectomy	14 (78)
Lobectomy en-bloc chest wall	1 (5)
Pneumonectomy[b]	3 (17)
Any complication[a,c]	2 (11)
Postoperative mortality	0
Clinical stage	
T2N0[d]	16 (80)
T1N1	1 (5)
T2N1	1 (5)
T2N2	2 (10)[e]

Values are given as *N* (%) or mean (range).
[a] Denominator $n = 18$, patients undergoing surgical resection.
[b] All were right-sided.
[c] Both were self-limiting atrial fibrillation.
[d] Median tumor size of this group was 4.0 cm.
[e] These two patients did not undergo surgery, see text for details.
FEV1, forced expiratory volume in 1 sec; DLCO, diffusion capacity of lung for carbon monoxide.

with pCR defined as complete necrosis of the tumor cells or the absence of any tumor cells. All pathology was reviewed by our thoracic study pathologist (B.A.). Survival was estimated by Kaplan-Meier method and compared using log-rank test. Our institutional review board approved of this prospective phase II trial, and written informed consent was obtained from all patients.

RESULTS

From 2004 to 2007, 20 patients were enrolled. Patient characteristics are given in Table 1. All 20 patients complete the prescribed three cycles of carboplatin and 16 of 20 patients received all 9 weeks of paclitaxel (four patients missed 1 week of paclitaxel). Toxicity of chemotherapy included grade 4 neutropenia in 1 (5%), grade 3 neutropenia in 3 (15%), grade 3 neuropathy in 1 (15%), and grade 3 nausea in 1 (5%). After chemotherapy, radiographic complete response was seen in 1 patient (5%), partial response in 7 (35%), stable disease in 12 (60%), and no patient had disease progression.

After chemotherapy, one patient refused surgery and received chemoradiation and one patient died of an unexpectedly nontreatment-related accidental event. These two patients not undergoing surgery both had clinical stage IIIA (T2N2). The 18 (90%) patients who underwent surgery all achieved complete resection as defined by the margin and the highest mediastinal node being free of tumor involvement. Of the 18 patient who underwent resection, pathology revealed 3 (17%) with pCR, one from each clinical stage of T2N0, T1N1, and T2N1 with each of these patients experiencing radiographic stable disease (1.9 cm), partial response (1.2 cm), and complete response, respectively. Including the 3 patients with pCR, a total of 7 (39%) patients were pathologically down-staged.

The median follow-up is 67 months. Overall survival for clinical stage IB, which represented the majority of our patients ($n = 16$), was 69% at 5 years with the median not yet reached. Overall survival was better for those patients who were down-staged (from clinical staging to pathologic staging) versus those who were not (100% versus 55% at 5 years, $p = 0.05$). The three patients with pCR also remain disease-free after follow-up of 68, 67, and 35 months.

DISCUSSION

In the treatment of early-stage lung cancer, a significant benefit for postoperative or adjuvant chemotherapy was seen in the National Cancer Institute of Canada JBR10[3] randomized trial. With longer follow-up of median more than 9 years, the positive results of JBR10 was reconfirmed by Butts et al.[8] However, the compliance of chemotherapy after surgery has been poor. The JBR10[5] showed only 50% compliance with the planned four cycles of postoperative chemotherapy. More recently, the Neoadjuvant Adjuvant Taxol Carboplatin Hope (NATCH)[9] randomized trial showed significantly better compliance with three cycles of chemotherapy when given preoperatively versus postoperatively (90% versus 61% respectively, $p < 0.001$). The recent Southwest Oncology Group (SWOG) 9900[10] randomized trial showed a 79% compliance rate with three cycles of preoperative chemotherapy. Furthermore, the neoadjuvant NATCH,[9] SWOG 9900,[10] and MRCLU22[11] trials have all shown no increase in operative morbidity and mortality in the setting of induction chemotherapy before surgery.

With data showing the advantages of preoperative chemotherapy delivery in terms of chemotherapy compliance without increasing surgical morbidity, we sought to determine whether the results of neoadjuvant therapy can be improved with a weekly paclitaxel chemotherapy regimen in a phase II trial. To our knowledge, there have been no published clinical trials assessing the delivery of weekly paclitaxel in the preoperative setting for early-stage lung cancer.

The use of weekly paclitaxel has been evaluated in patients with advanced-stage lung cancer. Trials by Belani et al.[12] and Socinski et al.[13] randomized delivering paclitaxel weekly versus every 3 weeks in combination with carboplatin for patients in stage IIIB and IV. A higher response rate ($p = 0.037$) was seen with weekly paclitaxel in the trial by Belani et al.,[12] with both trials showing no difference in the time to progression and the overall survival. However, less chemotherapy toxicity was suggested with weekly paclitaxel. A lower incidence of neuropathy, neutropenia, myalgia/arthralgia, and alopecia was seen while there was a higher incidence of anemia. Socinski et al.[13] also showed better quality of life and less taxane-related side effects with the weekly regimen.

The results of our trial compares favorably with other published trials. Patients receiving our weekly preoperative

regimen had good compliance, favorable toxicity profile, and low surgical morbidity as compared with the standard regimen of paclitaxel every 3 weeks. The 40% radiographic response rate (5% complete, 35% partial) seen in our trial is similar to that seen in the NATCH,[9] SWOG 9900,[10] and MRCLU22[11] trials (53%, 41%, and 49% respectively). Our pCR rate of 17% also compares favorably with the same three trials mentioned above (10%, 9%, and 4%, respectively). Overall, 5-year survival of 69% in our trial for clinical stage IB also compares favorably with published data. The CALBG 9633[4] adjuvant trial for stage IB saw a 5-year overall survival of 60% for the treatment group, keeping in mind that this result was based on pathologic staging which incurs a survival advantage over clinical staging used in preoperative trials like ours. The American Joint Committee on Cancer Staging 6th edition staging of lung cancer by Mountain[2] showed a 38% 5-year overall survival for clinical stage IB. The current 7th edition staging system purposed by Goldstraw et al.,[14] which removed large tumors >5 cm from stage IB, showed a 5-year overall survival of 43% for clinical IB.

Our study has several limitations. First, this is not a randomized trial and comparison with other studies is for the purpose of discussion and any conclusions from such comparison should be accepted with caution. Second, the number of patients in our trial is small. With the publication of randomized trials establishing benefit of adjuvant chemotherapy in resected early-stage lung cancer, it became difficult to accrue to our neoadjuvant trial. This explains the 3-year period needed to accrue the 20 patients. Third, our conclusion regarding improved survival in patients with pathologic down-staging should also be taken with some caution. Although all patients analyzed were clinical stage IB or II, the two groups (down-staged versus not down-staged) may not be comparable due to the inherent inaccuracies of clinical staging. The diminished survival for patient who did not achieve pathologic down-staging may merely be due to the fact that they began at a higher stage (not detected clinically) rather than from the lack of chemotherapy effect. Although the same could be said regarding those who were down-staged (i.e., these patients were always at a lower stage and was inaccurately staged clinically), we are confident that down-staging due to chemotherapy effect truly did occur as these patients were all down-staged by either pCR or by tumor size becoming ≤3 cm (i.e., T2 to T1). The possible inaccuracy of clinical staging in neoadjuvant trials can lead to inequality between patient groups, and only through a randomized trial this can be corrected.

In conclusion, preoperative chemotherapy with weekly paclitaxel in combination with carboplatin is well tolerated and does not increase postoperative morbidity and mortality. This regimen achieves pCR and survival rates that compares favorably with every 3 weekly induction regimens and merit further investigation.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
2. Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710–1717.
3. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589–2597.
4. Strauss GM, Herndon JE II, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043–5051.
5. Alam N, Shepherd FA, Winton T, et al. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer. An analysis of National Cancer Institute of Canada and intergroup trial JBR.10 and a review of the literature. *Lung Cancer* 2005;47:385–394.
6. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176–181.
7. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–216.
8. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol* 2010;28:29–34.
9. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* 2010;28:3138–3145.
10. Pisters KM, Vallières E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. *J Clin Oncol* 2010;28:1843–1849.
11. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* 2007;369:1929–1937.
12. Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. *J Clin Oncol* 2008;26:468–473.
13. Socinski MA, Ivanova A, Bakri K, et al. A randomized phase II trial comparing every 3-weeks carboplatin/paclitaxel with every 3-weeks carboplatin and weekly paclitaxel in advanced non-small cell lung cancer. *Ann Oncol* 2006;17:104–109.
14. Goldstraw P, Crowley J, Chansky K, et al. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–714.